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(54) Title: METHOD FOR TREATING MIGRAINE HEADACHES

(57) Abstract

The present invention is related to a method of treating migraine headaches, preferably migraines such as those caused by cortical spreading depression, with an effective amount of a low affinity NMDA receptor antagonist. Suitable low affinity NMDA receptor antagonists are benzmorphan derivatives and analogs, such as those described herein. Suitable low affinity NMDA receptor antagonists are 3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-8-yl-3-[(pyridinyl carbonyl)oxy]-3-benzocine, metazocine, normetazocine, cyclazocine, norcyclazocine, alazocine, 1-N-allylnormetazocine, and phenazocine and pharmaceutically acceptable salts thereof.

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METHOD FOR TREATING MIGRAINE HEADACHES

This application is a continuation-in-part application of Serial No. 08/138,682, filed October 18, 1993, which is a continuation-in-part of Serial No. 08/115,510, filed September 1, 1993.

FIELD OF THE INVENTION

This invention relates to the treatment of headaches, in particular, migraine headaches in mammals, preferably humans, by the use of low affinity NMDA (N-methyl-D-aspartate) receptor antagonists.

BACKGROUND OF THE INVENTION

Cortical spreading depression (CSD), originally described by Leáo, A.A.P., J. Neurophysiol., Vol. 7, pp. 359-390, (1944), is associated with the propagation (2-6 mm/s) of transient changes in electrical activity, ionic homeostasis, circulation, and glucose and arachidonic acid metabolism in the affected hemisphere. See, for example, Lauritzen, M., Acta Neurol. Scand., Vol. 76, (Suppl. 113) pp. 4-40,(1987). Numerous experimental stimuli, when applied to the cortex, can reliably elicit CSD, e.g. penetrating and conclusive brain injury, excitatory amino acids, electrical stimulation and KCl (See also, Lauritzen, M. Path. Biol., Vol. 40, pp. 332-337, (1992)). Evidence supports the proposal that CSD is an important phenomenon in the pathophysiology of migraine with aura (Tepley *et al.*, *In* Biomagnetism, ed. by S. Williamson, L. Kaufmann, pp. 327-330, Plenum Press, New York, (1990)) and that glutamate plays a role in the initiation/propagation of CSD (Van Harreveld, A, J. Neurochem., Vol. 3, pp. 300-315, (1959)). In this regard, glutamate has been shown to be released during CSD and N-methyl-D-aspartate (NMDA), a glutamate receptor subtype agonist, potently triggers CSD (Curtis *et al.*, Nature, Vol. 191, pp. 1010-1011, (1961) and Lauritzen *et al.*, Brain Res., Vol. 475, pp. 317-327 (1988)).

Limited numbers of compounds have been proven efficacious in the treatment of migraines, therefore, demonstrating the necessity for new therapeutic treatments.

SUMMARY OF THE INVENTION

The present invention is to a method of treating migraine headaches, preferably migraines such as those caused by cortical spreading depression, with an effective amount of a low affinity NMDA receptor antagonist. Suitable low affinty NMDA receptor antagonists are benzmorphan derivatives, such as those described in formula (I) below.

DETAILED DESCRIPTION OF THE FIGURES

Figure 1. Cortical spreading depression (CSD) in the anesthetized rat. This schematic illustration of the experimental preparation shows the orientation of the laser doppler blood flow probes (LDF1 and LDF2) used to monitor cortical perfusion (CP1 and CP2) changes (B) in the parietal cortex. KCl microinjections were used to elicit CSD and blood pressure (BP), CP1, CP2 and EEG were monitored continually.

Figure 2. A typical analysis of EEG changes associated with CSD. The total EEG power between 1 and 16 Hz was reduced transiently by CSD (A) with differential effects on the frequency bands (1-4Hz, 4-8Hz, 8-12Hz, and 12-16Hz) composing the EEG (B). CSD caused the greatest percentage of the power to shift from the 4-8Hz band to the 1-4Hz band (B). Arrows indicate the cortical microinjection of 1M KCL (150 nl) and each column represents a 10 second sampling period (1 period/20 seconds).

Figure 3. Typical polygraph recordings demonstrating the effects of CSD on CP1, CP2 and EEG prior to (A) and 30, 60, and 90 min after (B, C, D) the administration of saline, MK-801 (hereinafter referred to as dizocilpine) or N-allylnormetazocine. Arrows indicate the cortical microinjection of 1M KCl (150 nl).

Figure 4. Dose-dependent inhibition of the CSD propagation rate. The effects of MK-801 and N-allylnormetazocine were determined 30 min following drug administration.

Figure 5. The dose-related time-course of the effects of MK-801 and N-allylnormetazocine on the CSD propagation rate. All doses of MK-801 and N-allylnormetazocine were administered approximately 8 min following the initial control CSD response (0 time). * indicates a significant change ($p<0.05$) in the CSD propagation rate when compared to initial control values.

DETAILED DESCRIPTION OF THE INVENTION

It has now been discovered that limited and selective inhibition of NMDA receptor mechanisms represents a novel therapeutic approach to the treatment of headaches, especially migraines in mammals, preferably humans.

The use of low affinity NMDA receptor antagonists have been shown to possess a time-course and toxicity profile which is more suitable for the treatment of headaches, especially migraines in mammals, preferably humans, than are agents acting similarly, but with high affinity. Specifically, in contrast to high affinity NMDA receptor antagonists, the low affinity NMDA receptor antagonists of the invention have a rapid onset of action (e.g., in the range of less than about 30 minutes) and a predictable dose-related duration of action.

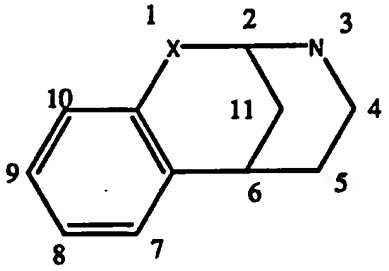
As defined herein, "low affinity NMDA receptor antagonists" means compounds which have a binding affinity (i.e., Kd) of about 100-fold less than the binding affinity of MK-801. Suitably, the Kd range is from about 200 nM to about 2000 nM. Preferably, the range is from about 400 to about 2000nM.

As defined herein, "high affinity NMDA receptor antagonists" means compounds which have a Kd binding affinity of less than 50 nM.

As defined herein, benzomorphan derivatives and analogs means a core benzomorphan structure as indicated below which is also often called a benzazocine core structure. The 8 membered ring may optionally have a carbon atom replaced by an oxygen or sulfur atom to form the benzoxozocine or benzothiazocin derivatives. The core structures are well known to those skilled in the art as these compounds date well back into the 1950's. The method of making these derivatives and analogs is well known in the art. Many patents teach making the various derivatives and substitutions of the core ring system, such as US Patent Nos. 3,033,867; 4,048,178; 3,345,373; and GB 1,044,853; Gordon et al., Nature, Vol. 192, p 1089 (1961); whose disclosures are incorporated by reference herein in their entirety. The core compounds such as metazocine, normetazocine, cyclazocine, norcyclazocine, alazocine, 1-N-allylnormetazocine, and phenazocine are only a few of the benzomorphan derivatives for use herein.

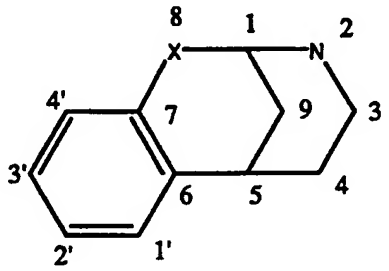
A core benzazocine (which is structurally synonymous with benzomorphan, however, which has a different ring numbering system), benzoxazocine and benzothiazocin

structure is as follows. The nomenclature used herein which recites "benzazocine" as the parent compound, is consistent with the ring numbering system depicted on the following core structural formula:



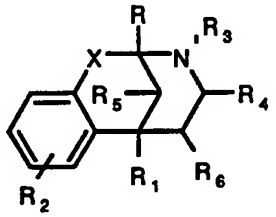
wherein X is carbon, oxygen or sulfur. The 8 membered ring may optionally contain a double bond; and the ring positions in the 8 membered ring may be optionally substituted. The benzene ring may also be optionally substituted.

The nomenclature used herein which recites "benzomorphan" as the parent compound, is consistent with the ring numbering system depicted on the following core structural formula:



wherein X is carbon, oxygen or sulfur. The 8 membered ring may optionally contain a double bond; and the ring positions in the 8 membered ring may be optionally substituted. The benzene ring may also be optionally substituted.

Such structures may be accorded the formula:



wherein
X is oxygen, sulfur, carbon, C=NOH or C=O;
R, R_1, and R_5 are independently selected from hydrogen or alkyl;
R_4 is hydrogen, =O or =S, alkyl, hydroxy, amino, or mono-alkyl amino;
R_3 is hydrogen, (optionally substituted) alkyl, (optionally substituted) hydroxyalkyl, alkenyl, dimethylallyl, (optionally substituted) aryl, (optionally substituted) arylalkyl, heteroarylalkyl, (optionally substituted) cycloalkylaryl, or hydroxy;
R_2 is hydrogen, hydroxy, alkoxy, arylalkyloxy, acetoxy, alkenyl, or 3-[(pyridinyl carbonyl) oxy];
R_6 is hydrogen, acetyl, carboxy, glyoxylic acid, glyoxylic acid ester derivatives, carbomethoxy, or ethoxycarbonylhydroxymethyl;
and pharmaceutically acceptable salts or hydrates thereof.

Optional subtituents for use herein include but are not limited to, hydroxy, alkyl, alkoxy, and amino. Preferred optional substituents for R_3 include 2,3-dihyroxy3-methylbutyl, 4-hydroxyphenylethyl, 4-methoxyphenethyl, 4-aminophenethyl, 1-hydroxy-cyclopropylmethyl.

Preferably R_3 is hydrogen, alkyl, aryl, arylalkyl, cycloalkylakyl, hydroxy, allyl. More preferably R_3 is hydrogen, methyl, phenyl, phenethyl, cyclopropylmethyl. Preferably X is oxygen, carbon, or C=O. More preferably X is carbon. Preferably R_2 is hydrogen, hydroxy, methoxy, benzyloxy, acetoxy, or 3-pyridine carboxylate. Preferably R, R_1 and R_5 are hydrogen or methyl. Preferably R_6 is hydrogen, acetyl, carboxy, glyoxylic acid, glyoxylic acid ester derivatives, carbomethoxy, ethoxycarbonylhydroxymethyl; alpha acetoxy acetic acid ethyl ester, alpha methoxy acetic acid ethyl ester, alpha 4-tosyloxy acetic acid ethyl ester, alpha 2-tosyloxy acetic acid ethyl ester, ethyl carbonyl hydroxy methyl, carboxymethoxy, with the proviso that when X is carbon, R, R_4 and R_6 are hydrogen, R_1 and R_5 are methyl, and R_2 is hydroxy, R_3 can not be $CH_2CH=C(CH_3)_2$ (i.e., a compound of the above formula that is commonly named pentazocine).

The terms "aryl" or "heteroaryl" are used herein at all occurrences to mean substituted and unsubstituted aromatic ring(s) or ring systems containing from 5 to 16 carbon atoms, which may include bi- or tri-cyclic systems and may include, but are not limited to heteroatoms selected from O, N, or S. Representative examples

include, but are not limited to, phenyl, naphthyl, pyridyl, quinolinyl, thiazinyl, and furanyl.

The terms "lower alkyl" or "alkyl" are used herein at all occurrences to mean straight or branched chain radical of 1 to 10 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

The term "alkenyl" is used herein at all occurrences to mean straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

The term alkyl in "aralkyl" or "heteroarylalkyl" is used herein to mean a C_{1-10} alkyl moiety as defined above.

Suitable well known derivatives for use herein include:
1,2,3,4,5,6-hexahydro-8-methoxy-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazocine;
1,2,3,4,5,6-hexahydro-8-(benzyloxy)-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocine;
2-[[1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(2-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-yl]oxy] ethanol;
1,2,3,4,5,6-hexahydro-8-(methoxymethoxy)-6,11-dimethyl-3-[alpha-ethyl-p(methylthio)benzyl]-2,6-methano-3-benzazocine;
1,2,3,4,5,6-hexahydro-8-(methoxymethoxy)-6,11-dimethyl-3-phenethyl-2,6-methano-3-benzazocine;
1,2,3,4,5,6-hexahydro-8-(methoxymethoxy)-6,11-dimethyl-2-phenethyl-2,6-methano-3-benzazocine;
1,2,3,4,5,6-hexahydro-8-(methoxymethoxy)-6,11-dimethyl-3-(p-aminophenethyl)-2,6-methano-3-benzazocine;
1,2,3,4,5,6-hexahydro-8-(methoxymethoxy)-6,11-dimethyl-3-(o-methoxyphenethyl)-2,6-methano-3-benzazocine;
1,2,3,4,5,6-hexahydro-8-(methoxymethoxy)-6,11-dimethyl-3-[2-(2-thienyl)ethyl]-2,6-methano-3-benzazocine; and
1,2,3,4,5,6-hexahydro-8-(methoxymethoxy)-6,11-dimethyl-3-[p-nitrophenethyl]-2,6-methano-3-benzazocine; and their pharmaceutically acceptable salts.

Other suitable benzomorphan derivatives and analogs, and their pharmaceutically acceptable salts, for use herein are:

(+/-)-Cyclazocine, 1,2,3,4,5,6-Hexahydro-3,6-dimethyl-2,6-methano-3-benzazocine hydrochloride, 1,2,3,4,5,6-Hexahydro-3,6-11-trimethyl-2,6-methano-3-benzazocine hydrochloride, 1,2,3,4,5,6-Hexahydro-3,6,11-trimethyl-2,6-methano-3-benzazocin-8-ol hydrochloride, (+)-1,2,3,4,5,6-Hexahydro-3,6,11-trimethyl-2,6-methano-3-benzazocin-8-ol hydrobromide, (-)-1,2,3,4,5,6-Hexahydro-3,6,11-trimethyl-2,6-methano-3-benzazocin-8-ol, (+)-1,2,3,4,5,6-Hexahydro-3,6,11-trimethyl-2,6-methano-3-benzazocin-8-ol, 1,2,3,4,5,6-Hexahydro-8-hydroxy-6,11-dimethyl-3-phenethyl-2,6-methano-3-benzazocine hydrobromide, d-1,2,3,4,5,6-Hexahydro-8-hydroxy-6,11-dimethyl-3-phenethyl-2,6-methano-3-benzazocine hydrobromide, (-)-1,2,3,4,5,6-Hexahydro-8-hydroxy-6,11-dimethyl-3-phenethyl-2,6-methano-3-benzazocine hydrobromide, 1,2,3,4,5,6-Hexahydro-3,6-dimethyl-2,6-methano-3-benzazocin-8-ol hydrochloride, 2-Ethyl-2'-hydroxy-5,9-dimethyl-6,7-benzmorphan hydrobromide, 2'-Hydroxy-5,9-dimethyl-6,7-benzmorphan hydrochloride, 5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan, 2'-Hydroxy-5,9-dimethyl-2-propyl-6,7-benzmorphan hydrochloride, 2'-Methoxy-2,5,9-trimethyl-6,7-benzmorphan hydrobromide, (+)-2'-Methoxy-2,5,9-trimethyl-6,7-benzmorphan hydrobromide, (-)-2'-Methoxy-2,5,9-trimethyl-6,7-benzmorphan hydrobromide, 3-Butyl-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocin-8-ol hydrobromide, 2'-Acetoxy-5,9-dimethyl-2-phenethyl-6,7-benzmorphan hydrobromide, 2'-Hydroxy-2,5,9-trimethyl-6,7-isobenzmorphan hydrochloride, 2'-Hydroxy-5,9-dimethyl-2-phenylpropyl-6,7-benzmorphan hydrochloride, 2'-Hydroxy-5,9-dimethyl-2-[2-(4-aminophenyl)ethyl]-6,7-benzmorphan, 2'-Hydroxy-5,9-dimethyl-2-[2-(2-thienyl)ethyl]-6,7-benzmorphan, 2'-Hydroxy-5,9-dimethyl-2-(2-phenylethyl)-6,7-benzmorphan hydrobromide, 2'-Methoxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide, (+)-2'-Methoxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide, (-)-2'-Methoxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide, 9-Hydroxy-2'-methoxy-2,5,9-trimethyl-6,7-benzmorphan hydrochloride, 2'-Hydroxy-5,9-dimethyl-2-(4-methoxyphenyl)ethyl-6,7-benzomorphan hydrobromide, 2'-Hydroxy-5,9-dimethyl-2-(4-hydroxyphenyl)ethyl-6,7-benzomorphan hydrobromide, 2'9-Dihydroxy-2,5,9-trimethyl-6,7-benzomorphan hydrobromide, 2'-Methoxy-5,9-dimethyl-2-allyl-6,7-benzmorphan hydrochloride, 2-Amyl-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan hydrochloride, 2'-(4-Nitrobenzoyl)oxy-3-(2-phenylethyl)-5,9-dimethyl-6,7-benzomorphan hydrochloride,

2'-Hydroxy-5,9-dimethyl-2-allyl-6,7-benzomorphan (diastereomers), [2S-(2-alpha,6-alpha,11R*)]-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride (or (+)-2'-Hydroxy-5,9-dimethyl-2-allyl-6,7-benzomorphan hydrochloride, which has the common name, (+)-N-Allylnormetazocine hydrochloride), [2R-(2-alpha,6-alpha,11R*)]-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride (or (-)-2'-Hydroxy-5,9-dimethyl-2-allyl-6,7-benzomorphan hydrochloride, which has the common name, (-)-N-Allylnormetazocine hydrochloride), (2-alpha,6-alpha,11R*)-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride (or 2'-Hydroxy-5,9-dimethyl-2-allyl-6,7-benzomorphan hydrochloride, which has the common name, N-Allylnormetazocine hydrochloride), 2'-Methoxy-5,9-dimethyl-2-phenacyl-6,7-benzomorphan hydrochloride, 1,2,3,4,5,6-Hexahydro-8-nicotinoyl-6,11-dimethyl-3-phenethyl-2,6-methano-3-benzazocin, 1,2,3,4,5,6-Hexahydro-8-nicotinoyl-6,11-dimethyl-3-phenethyl-2,6-methano-3-benzazocin maleate, alpha-9-Hydroxy-2,5-dimethyl-6,7-benzomorphan hydrobromide, alpha-9-Acetoxy-2,5-dimethyl-6,7-benzomorphan hydrobromide, 5,9-Diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan hydrochloride, alpha-(+)-5,9-Diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan hydrochloride, alpha-2',9-Diacetoxy-2,5-dimethyl-6,7-benzomorphan hydrobromide, 5-Ethyl-2'-hydroxy-2-phenethyl-6,7-benzomorphan hydrochloride, 5-Ethyl-2'-hydroxy-2-methyl-6,7-benzomorphan hydrochloride, 2'-Hydroxy-2,5-dimethyl-9-ethyl-6,7-benzomorphan hydrochloride, 2'-Hydroxy-2-methyl-5-propyl-6,7-benzomorphan hydrochloride, alpha-2-Methyl-2'-hydroxy-5,9-dipropyl-6,7-benzomorphan hydrochloride, 2,5-Dimethyl-6,7-benzomorphan hydrobromide, Methoxymethylphenazocine, 5,9-Diethyl-2-methyl-6,7-benzomorphan hydrochloride (or 6,11-Diethyl-1,2,3,4,5,6-hexahydro-3-methyl-2,6-methano-3-benzazocine monohydrochloride), 2,5-Dimethyl-8-oxo-6,7-benzomorphan, methobromide, 2'-Hydroxy-5,9-dimethyl-2,2-dimethylallyl-6,7-benzomorphan, 2-[4-(4'-Fluoro)butyrophenone)-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan, 2'-Benzyloxy-2-allyl-5,9-dimethyl-6,7(H)benzomorphan hydrochloride, 5,9-Dimethyl-2-(3,3-dimethylallyl)-2'-benzyl-(alpha-14C)oxy-6,7-benzomorphan hydrobromide, 3,4,5,6-Tetrahydro-2,3-dimethyl-4-oxo-2,6-methano-2H-1,3-benzoxazocin-5-glyoxylic acid ethyl ester, 5-Carboxy-2-ethyl-2,6-methano-3-methyl-4-oxo-2,3,4,5,6-pentahydro-1,3-benzoxacine, 5-Acetyl-2-methyl-4-oxo-2,6-methano-2,3,4,5,6-pentahydro-1,3-benzoxazocine, 2,3-Dimethyl-4-thioxo-3,4,5,6-tetrahydro-2,6-methano-2H-1,3-benzothiazocin, 2-Ethyl-3,9-dimethyl-10-oxo-11-carboxy-2,4-(iminoethano)-3,4-dihydro-2H-1-benzopyran, 2,3-Dimethyl-4-oxo-2-ethano-2,3,4,5,6-pentahydro-1,3-

benoxazocine-alpha-O-tosylacetic acid ethyl ester, 2,6-Methano-2,3-dimethyl-4-oxo-2,3,4,5-tetrahydro-6H-1,3-benzoxazocine, 2,9-Dimethyl-10-oxo-11-carbomethoxy-3,4-dihydro-2,4-(iminoethano)-2H-1-benzopyran, 2,3-Dimethyl-2,6-methano-4-oxo-2,3,4,5,6-pentahydro-1,3-benzoxazocine-5-carboxylic acid ethyl ester, 2-Phenyl-3-methyl-4-oxo-5-carboxy-2,6-methano-2,3,4,5,6-pentahydro-1,3-benzoxazocine, 5-(Ethoxycarbonylhydroxymethyl)-2,3,4,5-tetrahydro-2,6-methano-2-methyl-4-oxo-3-phenyl-6H-1,3-benzoxazocine, 1,4-Dioxo-5-(ethylcarbonylhydroxymethyl)-1,2,3,4,5,6-hexahydro-2,6-methano-2-methyl-3-phenyl-benzazocine, 2,3-Dimethyl-4-oxo-2,6-methano-2,3,4,5-tetrahydro-6H-1,3-benzoxazocine-5-[alpha-(4-tosyloxy)acetic acid], ethyl ester, 2-Methyl-4-oxo-3-phenyl-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocine, 6-Dimethyl-2,6-methano-4-oxo-2,3,4,5-tetrahydro-6H-1,3-benzoxazocine-5-carboxylic acid, 2-Ethyl-2,6-methano-3-methyl-4-oxo-2,3,4,5-tetrahydro-6H-1,3-benzoxazocine, 2-Ethyl-3,11-dimethyl-2,6-methano-2,3,4,5-tetrahydro-6H-1,3-benzoxazocin-4-one, 2,3-Dimethyl-4-oxo-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocine-5-glyoxylic acid, 3-Methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocine, 2,3-Dimethyl-2,6-methano-4-oxo-2,3,4,5-tetrahydro-6H-1,3-benzoxazocine-5-ylidene-5-(alpha-methoxy)acetic acid, ethyl ester, 2,3-Dimethyl-2,6-methano-4-oxo-2,3,4,5-tetrahydro-6H-1,3-benzoxazocine-5-(alpha-acetoxy)acetic acid, ethyl ester, 2-Methyl-3-phenyl-4-oxo-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocin-delta-5-alpha-acetic acid, 2-Methyl-3-phenyl-4-oxo-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocine-5-(alpha-acetoxyacetic acid ethyl ester), 2-Methyl-4-oxo-3-phenyl-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocine-5-phenylhydrazanoacetic acid ethyl ester, 2-Ethyl-3-hydroxy-4-oxo-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocine, 2-Methyl-3-hydroxy-4-oxo-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocine, 2-Methyl-4-oxo-3-phenyl-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocine-delta-5-alpha-acetic acid ethyl ester, 2-Methyl-4-(methylamino)-2,3-dihydro-2,6-methano-1,3-benzoxazocine, 3,4,5,6-Tetrahydro-3,6-dimethyl-2,6-methano-3-benzazocine, 1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(2,3-dihydroxy-3-methylbutyl)-2,6-methano-3-benzozocine-8-ol hydrochloride, 3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocin-8-yl-3-[(pyridinyl carbonyl)oxy] hydrochloride (or 2-(Cyclopropylmethyl)-5,9-dimethyl-3'-nicotinoyloxybenzomorphanhydrochloride (3:4) or 3-(Cyclopropylmethyl)-6,11-dimethyl-2,6-methano-8-nicotinoyloxy-1,2,3,4,5,6-hexahydrobenzazocine hydrochloride), 3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocin-8-yl 3-pyridinecarboxylate dihydrobromide (or 2-(Cyclopropylmethyl)-5,9-dimethyl-3'-

nicotinoyloxybenzomorphan dihydrobromide) (+)-2-(Cyclopropylmethyl)-5,9-dimethyl-3'-nicotinoyloxybenzomorphan, hydrobromide (which has the common name Nicotinoyloxycyclazocine), N-Cyclopropylmethyl-5,9-dimethyl-3'-hydroxybenzomorphan (which has the common name, Cyclazocine), Ethylketocyclazocine methanesulfonate, Ketocyclazocine base, or (+/-)Bremazocine and the pharmaceutically acceptable salts, and hydrates thereof.
Preferred compounds for use herein include 3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-8-yl-3-[(pyridinyl carbonyl)oxy]-3-benzazocine, metazocine, normetazocine, cyclazocine, norcyclazocine, alazocine, 1-N-allylnormetazocine, and phenazocine and pharmaceutically acceptable salts and hydrates thereof.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are included within the scope of the present invention.

CSD can be blocked by competitive and noncompetitive NMDA antagonists, suggesting that NMDA receptor mechanisms mediate the initiation and/or propagation of CSD (Marannes, *et al.*, Evidence for a role of the N-methyl-D-aspartate receptor in cortical spreading depression in the rat, Brain Res. **457** pp. 226-240 (1988); and Lauritzen *et al*, see also the effect of glutamate receptor blockade on anoxic depolarization and cortical spreading depression, J. Cereb. Blood Flow Metab. **12** pp. 223-229 (1992)).

The prototypic sigma-agonist, N-allylnormetazocine, is neuroprotective against the excitotoxic action of glutamate in vitro and following transient forebrain ischemia in the gerbil (Lysko *et al.*, Stroke, Vol. 23, pp. 1319-1224 (1992)). The neuroprotective mechanism of (+) N-allylnormetazocine is probably related to its action as a noncompetitive NMDA receptor channel antagonist (Lodge *et al.*, Trends Neurosci., Vol. 11, pp. 81-86,(1990); and Lysko *et al.*, Neurosci. Lett., Vol. 120, pp. 217-220 (1990)) and capable of blocking cation influx initiated by glutamate and aspartate (Lysko *et al.*, Stroke, Vol. 23, pp. 414-419 (1992a); and Lysko *et al.*, Stroke, Vol. 23, pp. 1319-1224 (1992b)) also found that at equivalent neuroprotective doses, the hypothermic and motor disturbances associated with N-allylnormetazocine were brief when compared to the protracted effects of MK-801, the most potent noncompetitive NMDA receptor channel antagonist available (Wong

et al., Proc. Natl. Acad. Sci. U.S.A., Vol. 83, pp. 7104-7108 (1986); and Wong *et al.*, J. Neurochem., Vol. 50, pp. 274-281 (1988).

The above noted observations may be related to the fact that MK-801 binds with high affinity (Kd=6 nM) to NMDA receptor channels in a use/voltage dependent manner (MacDonald *et al.*, Trends Neurosci., Vol. 11, pp. 167-172 (1990); Rogawski *et al.*, J. Pharmacol. Exp. Ther., Vol. 259, pp. 30, 37 (1991); and Jones *et al.*, Mol. Neuropharm., Vol. 2, pp. 303-310 (1992)), whereas, (+) N-allylnormetazocine is an equieffective inhibitor of the NMDA receptor channel, but binds with much lower affinity (Kd=475 nM) to the MK-801 site (Lysko *et al.*, *In* Proceedings of the International Workshop on Glutamate-Transmitter and Toxin, ed. by O. Kempski, in press, 1993).

NMDA-mediated neurotransmission is essential for the propagation of CSD and represents an important patho-mechanism in migraine. CSD was elicited by the intracortical microinjection of 1M KCl (150 nl) in the anesthetized rat and the propagation rate was determined by monitoring the hyperemic response associated with CSD along the ipsilateral parietal cortex. The electroencephalogram (EEG) was also monitored continually in each experiment. In control experiments, CSD elicited a consistent transient (<10 min) reduction in total EEG power and the CSD propagation rate did not change significantly over a 4 hour observation period when CSD was evoked at 30 min intervals. MK-801 and (+) N-allylnormetazocine caused a dose-related inhibition of the EEG suppression and cortical hyperemia associated with CSD and reduced the CSD propagation rate; ED_{50}=1 mg/kg, iv and 15 mg/kg, iv, respectively. MK-801 had a delayed onset of action (inversely related to dose) and a prolonged duration of action at all doses (>2 h). In contrast, (+) N-allylnormetazocine had a rapid onset of action (<30 min) and a predictable dose-related duration of action.

The following methodologies characterize and compare the dose-response relationship and time-course of action of (+) N-allylnormetazocine and MK-801 on CSD. Specifically, changes in the propagation rate, EEG power and cortical perfusion (CP) were determined in the anesthetized rat.

Methods

General Surgical Preparation. Twenty-four male Sprague-Dawley rats weighing 350-375 g were housed in a thermally controlled (25°C), 12-hour light-cycled (6 AM

to 6 PM) laboratory animal facility with free access to food and water until the day of experimentation. The general surgical procedure has been described previously (Willette *et al.*, Stroke, Vol. 21, pp. 451-458 (1990)). Briefly, surgical anesthesia was induced with 2.5% isoflurane in 100% O_2. The left femoral artery was cannulated with polyethylene tubing for the continuous measurement of arterial blood pressure and periodic sampling of arterial blood gases. The femoral vein was prepared similarly for the intravenous administration of drugs. A tracheostomy was performed and the isoflurane anesthesia was discontinued. Anesthesia was then maintained by slowly administering pentobarbital (40 mg/kg, i.v.) over the next 10 minutes. This procedure provides stable anesthesia for at least 1 hour. Lidocaine ointment (5%) was applied to the femoral and cervical incisions prior to closing with wound clips. Anesthesia and a stable blood pressure and heart rate were maintained for approximately 3-4 hours by administering supplemental doses of pentobarbital (10 mg/kg, i.v.) at 30 min intervals (approximately).

Cortical Spreading Depression. Each rat was placed prone in a stereotaxic instrument (DKI, Tujunga, California) and secured in a flat skull position. A small thermostatic heating pad was placed beneath the abdomen to maintain rectal temperature at 37-38°C for the remainder of the experiment. The right frontal and parietal bones were exposed and rostral, intermediate and caudal burr holes (2 mm dia.) were prepared with the dura intact (see Fig. 1A). Each rat was then paralyzed with tubocurarine (1 mg/kg, i.v.) and ventilated artificially with a rodent respirator (Harvard Apparatus, South Natick, Massachusetts) at a rate of 75 breaths per min and a volume of 3-4 ml/breath. Automated blood gas analysis was performed periodically and ventilation parameters were adjusted to maintain arterial $PaCO_2$, PaO_2 and pH within the ranges of 33.5-38 mm Hg, >75 mm Hg and 7.35-7.45, respectively. Micromanipulators were used to place Laser-Doppler Flowmetry (LDF) needle probes (LF21, Transonic Systems, Inc., Ithaca, NY) 4 mm apart in the intermediate and rostral cranial windows (Fig. 1A) and local cortical perfusion (CP) was monitored continuously. The stainless steel housing of each probe was used for recording the EEG. EEG power was determined between 1 and 16Hz as described previously (Willette *et al.*, Stroke, Vol. 23, pp. 703-711 (1992)). A third micromanipulator was used to position a glass micropipette (40 μm O.D.) 0.5 mm beneath the cortical surface in the caudal cranial window. Following a 20-30 minute acclimation period, CSD was elicited by microinjecting 1M KCl (150 nl) at the caudal site. Vehicle or drugs were administered intravenously after the electrical and cerebrovascular effects of the initial CSD had subsided (8-10 min after KCl

microinjection). The microinjection of KCl was then repeated every 30 min for at least 2 hours and the changes in CP, EEG power and propagation rate associated with CSD were determined.

Preparation and administration of drugs. All drugs were prepared in saline and administered by the intravenous route in volumes not exceeding 0.3 ml. (+) N-allylnormetazocine and (-)N-allylnormetazocine were obtained from NIDA (Rockville, MD) and (+)MK-801 was obtained from RBI (Natick, MA).

Statistical analysis. Multiple comparisons with control values were evaluated with an ANOVA for repeated measures followed by post hoc analysis with the Bonferroni two-tailed *t* test (Wallenstein *et al.*, Circ. Res., Vol. 47, pp. 1-9 (1980)). The dose needed to cause a 50% reduction in the CSD propagation rate (ED_{50}) was determined graphically. All summary values were expressed as mean ± SEM, and differences were considered significant at $p \leq 0.05$.

Characterization of the CSD response. The cortical microinjection (150 nl) of KCl (1M) elicited CSD in the rat (Fig. 1). CSD was associated with a slight reduction in CP followed rapidly by a large transient hyperemia and a delayed prolonged (approximately 30 min) oligemia (approximately 20 reduction in CP). A reduction in the EEG power, particularly at the higher frequencies (>4 Hz), accompanied the hyperemic response (Fig. 2). With the exception of the oligemic phase, which was observed only after the initial CSD, the responses associated with CSD were highly reproducible when elicited with KCl at 30 min intervals for up to 4 hrs (Fig. 3, saline). No significant effects on arterial blood pressure or heart rate were observed.

The delay in the onset of the hyperemic response between the caudal and rostral LDF probe was used to calculate the rate of CSD propagation. The basal propagation rate was 3.7±0.12 mm/min. In vehicle (saline) treated animals (n=4), the rate of CSD propagation did not change significantly when evoked repeatedly over 4 hrs (Fig. 3, saline).

Effects of MK-801 on CSD. The administration of MK-801 caused a dose-related (0.3-3.0 mg/kg, i.v.) inhibition in the rate of CSD propagation (Figs. 3, 4 & 5). The ED_{50} for MK-801 was approximately 1 mg/kg (i.v.) at 30 minutes (Fig. 4). The duration of the blockade elicited by MK-801 was prolonged (>2 hrs) and complete at the higher doses (Figs. 3&5). However, the action of MK-801 was delayed in onset.

At low doses, MK-801 reduced the rate of CSD propagation slowly and actually prolonged the hyperemic response associated with CSD in some cases.

Effects of (+) N-allylnormetazocine on CSD. Like MK-801, (+) N-allylnormetazocine caused a dose-related (3-60 mg/kg) inhibition of CSD following intravenous administration with an ED_{50} of 15 mg/kg, i.v. (Figs. 3, 4 & 5). However, the time-course of action differed markedly for MK-801 and (+) N-allylnormetazocine. The onset and maximum effect observed with (+) N-allylnormetazocine occurred within 30 min of administration at all doses (Fig. 5). The duration of action of (+) N-allylnormetazocine was dose-related and relatively brief; CSD recovered completely within 1 hour following a maximally effective dose (30 mg/kg, i.v.). At the highest dose tested (60 mg/kg, i.v.), (+) N-allylnormetazocine inhibited CSD for > 90 min. Low doses of (+) N-allylnormetazocine caused a brief, gradual reduction in the rate of CSD propagation and increased the duration of the hyperemic response. (-) N-allylnormetazocine also inhibited CSD propagation completely, but only at 60 mg/kg, i.v.

Formulation of Pharmaceutical Compositions

The pharmaceutically effective compounds of this invention are administered in conventional dosage forms prepared by combining a compound of formula (I) ("active ingredient") in an amount sufficient to treat headaches, in particular migraine headaches, such as those caused by cortical spreading depression, with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg. to about 1000 mg. When a liquid

carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

This invention relates to a method of treating headaches, in particular migraine headaches, such as those caused by cortical spreading depression, in a mammal in need thereof, including humans, which comprises administering to such mammal an effective amount of a low affinity NMDA receptor antagonist as depicted in formula (I).

By the term "treating" is meant either prophylactic or therapeutic therapy. Such formula (I) compound can be administered to such mammal in a conventional dosage form prepared by combining the formula (I) compound with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The formula (I) compound is administered to a mammal in need of treatment for headaches, in particular migraine headaches, specifically those caused by cortical spreading depression, in an amount sufficient to decrease pain associated with the headache. The route of administration may be oral or parenteral.

The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intra-rectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The daily parenteral dosage regimen will preferably be from about 30 mg to about 300 mg per day of active ingredient [i.e., the compound of formula (I)]. The daily oral dosage regimen will preferably be from about 100 mg to about 2000 mg per day of active ingredient.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a formula (I) compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the Formula (I) compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration it is believed that one skilled in the art can, use the preceding description, utilize the present invention to its fullest extent. Therefore any examples are to be construed as merely illustrative and not a limitation on the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A method of treating headaches in a mammal in need of such treatment which method comprises administering to said mammal an effective amount of a low affinity NMDA receptor antagonist, provided that the low affinity NMDA receptor antagonist is not pentazocine.

2. The method as claimed in claim 1 wherein the headache is migraine in origin.

3. The method as claimed in claim 1 wherein the compound is N-allylnormetazocine.

4. The method as claimed in claim 1 wherein the compound is metazocine.

5. The method as claimed in claim 1 wherein the compound is cyclazocine.

6. The method as claimed in claim 1 wherein the low affinity NMDA receptor antagonist binds in the range from about 200nM to about 2000nM.

7. The method as claimed in claim 1 wherein the low affinity NMDA receptor antagonist binds in the range from about 400nM to about 2000nM.

8. The method according to Claim 1 wherein the low affinity NMDA receptor antagonist is selected from:
1,2,3,4,5,6-hexahydro-8-methoxy-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazocine;
1,2,3,4,5,6-hexahydro-8-(benzyloxy)-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocine;
2-[[1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(2-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-yl]oxy] ethanol;
1,2,3,4,5,6-hexahydro-8-(methoxymethoxy)-6,11-dimethyl-3-[alpha-ethyl-p(methylthio)benzyl]-2,6-methano-3-benzazocine;
1,2,3,4,5,6-hexahydro-8-(methoxymethoxy)-6,11-dimethyl-3-phenethyl-2,6-methano-3-benzazocine;

1,2,3,4,5,6-hexahydro-8-(methoxymethoxy)-6,11-dimethyl-2-phenethyl-2,6-methano-3-benzazocine;
1,2,3,4,5,6-hexahydro-8-(methoxymethoxy)-6,11-dimethyl-3-(p-aminophenethyl)-2,6-methano-3-benzazocine;
1,2,3,4,5,6-hexahydro-8-(methoxymethoxy)-6,11-dimethyl-3-(o-methoxyphenethyl)-2,6-methano-3-benzazocine;
1,2,3,4,5,6-hexahydro-8-(methoxymethoxy)-6,11-dimethyl-3-[2-(2-thienyl)ethyl]-2,6-methano-3-benzazocine; and
1,2,3,4,5,6-hexahydro-8-(methoxymethoxy)-6,11-dimethyl-3-[p-nitrophenethyl]-2,6-methano-3-benzazocine; and their pharmaceutically acceptable salts.

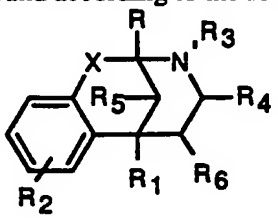
9. The method according to Claim 1 wherein the low affinity NMDA receptor antagonist is selected from:
(+/-)-Cyclazocine, 1,2,3,4,5,6-Hexahydro-3,6-dimethyl-2,6-methano-3-benzazocine hydrochloride, 1,2,3,4,5,6-Hexahydro-3,6-11-trimethyl-2,6-methano-3-benzazocine hydrochloride, 1,2,3,4,5,6-Hexahydro-3,6,11-trimethyl-2,6-methano-3-benzazocin-8-ol hydrochloride, (+)-1,2,3,4,5,6-Hexahydro-3,6,11-trimethyl-2,6-methano-3-benzazocin-8-ol hydrobromide, (-)-1,2,3,4,5,6-Hexahydro-3,6,11-trimethyl-2,6-methano-3-benzazocin-8-ol, (+)-1,2,3,4,5,6-Hexahydro-3,6,11-trimethyl-2,6-methano-3-benzazocin-8-ol, 1,2,3,4,5,6-Hexahydro-8-hydroxy-6,11-dimethyl-3-phenethyl-2,6-methano-3-benzazocine hydrobromide, d-1,2,3,4,5,6-Hexahydro-8-hydroxy-6,11-dimethyl-3-phenethyl-2,6-methano-3-benzazocine hydrobromide, (-)-1,2,3,4,5,6-Hexahydro-8-hydroxy-6,11-dimethyl-3-phenethyl-2,6-methano-3-benzazocine hydrobromide, 1,2,3,4,5,6-Hexahydro-3,6-dimethyl-2,6-methano-3-benzazocin-8-ol hydrochloride, 2-Ethyl-2'-hydroxy-5,9-dimethyl-6,7-benzmorphan hydrobromide, 2'-Hydroxy-5,9-dimethyl-6,7-benzmorphan hydrochloride, 5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan, 2'-Hydroxy-5,9-dimethyl-2-propyl-6,7-benzmorphan hydrochloride, 2'-Methoxy-2,5,9-trimethyl-6,7-benzmorphan hydrobromide, (+)-2'-Methoxy-2,5,9-trimethyl-6,7-benzmorphan hydrobromide, (-)-2'-Methoxy-2,5,9-trimethyl-6,7-benzmorphan hydrobromide, 3-Butyl-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocin-8-ol hydrobromide, 2'-Acetoxy-5,9-dimethyl-2-phenethyl-6,7-benzmorphan hydrobromide, 2'-Hydroxy-2,5,9-trimethyl-6,7-isobenzmorphan hydrochloride, 2'-Hydroxy-5,9-dimethyl-2-phenylpropyl-6,7-benzmorphan hydrochloride, 2'-Hydroxy-5,9-dimethyl-2-[2-(4-aminophenyl)ethyl]-6,7-benzmorphan, 2'-Hydroxy-5,9-dimethyl-2-[2-(2-thienyl)ethyl]-6,7-benzmorphan, 2'-Hydroxy-5,9-dimethyl-2-(2-phenylethyl)-6,7-benzmorphan hydrobromide, 2'-Methoxy-5,9-dimethyl-2-phenethyl-6,7-

benzomorphan hydrobromide, (+)-2'-Methoxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide, (-)-2'-Methoxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide, 9-Hydroxy-2'-methoxy-2,5,9-trimethyl-6,7-benzmorphan hydrochloride, 2'-Hydroxy-5,9-dimethyl-2-(4-methoxyphenyl)ethyl-6,7-benzomorphan hydrobromide, 2'-Hydroxy-5,9-dimethyl-2-(4-hydroxyphenyl)ethyl-6,7-benzomorphan hydrobromide, 2'9-Dihydroxy-2,5,9-trimethyl-6,7-benzomorphan hydrobromide, 2'-Methoxy-5,9-dimethyl-2-allyl-6,7-benzmorphan hydrochloride, 2-Amyl-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan hydrochloride, 2'-(4-Nitrobenzoyl)oxy-3-(2-phenylethyl)-5,9-dimethyl-6,7-benzomorphan hydrochloride, 2'-Hydroxy-5,9-dimethyl-2-allyl-6,7-benzomorphan (diastereomers), [2S-(2-alpha,6-alpha,11R*)]-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride (or (+)-2'-Hydroxy-5,9-dimethyl-2-allyl-6,7-benzomorphan hydrochloride, which has the common name, (+)-N-Allylnormetazocine hydrochloride), [2R-(2-alpha,6-alpha,11R*)]-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride (or (-)-2'-Hydroxy-5,9-dimethyl-2-allyl-6,7-benzomorphan hydrochloride, which has the common name, (-)-N-Allylnormetazocine hydrochloride), (2-alpha,6-alpha,11R*)-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride (or 2'-Hydroxy-5,9-dimethyl-2-allyl-6,7-benzomorphan hydrochloride, which has the common name, N-Allylnormetazocine hydrochloride), 2'-Methoxy-5,9-dimethyl-2-phenacyl-6,7-benzomorphan hydrochloride, 1,2,3,4,5,6-Hexahydro-8-nicotinoyl-6,11-dimethyl-3-phenethyl-2,6-methano-3-benzazocin, 1,2,3,4,5,6-Hexahydro-8-nicotinoyl-6,11-dimethyl-3-phenethyl-2,6-methano-3-benzazocin maleate, alpha-9-Hydroxy-2,5-dimethyl-6,7-benzomorphan hydrobromide, alpha-9-Acetoxy-2,5-dimethyl-6,7-benzomorphan hydrobromide, 5,9-Diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan hydrochloride, alpha-(+)-5,9-Diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan hydrochloride, alpha-2',9-Diacetoxy-2,5-dimethyl-6,7-benzomorphan hydrobromide, 5-Ethyl-2'-hydroxy-2-phenethyl-6,7-benzomorphan hydrochloride, 5-Ethyl-2'-hydroxy-2-methyl-6,7-benzomorphan hydrochloride, 2'-Hydroxy-2,5-dimethyl-9-ethyl-6,7-benzomorphan hydrochloride, 2'-Hydroxy-2-methyl-5-propyl-6,7-benzomorphan hydrochloride, alpha-2-Methyl-2'-hydroxy-5,9-dipropyl-6,7-benzomorphan hydrochloride, 2,5-Dimethyl-6,7-benzomorphan hydrobromide, Methoxymethylphenazocine, 5,9-Diethyl-2-methyl-6,7-benzomorphan hydrochloride (or 6,11-Diethyl-1,2,3,4,5,6-hexahydro-3-methyl-2,6-methano-3-benzazocine monohydrochloride), 2,5-Dimethyl-8-oxo-6,7-benzomorphan, methobromide, 2'-Hydroxy-5,9-dimethyl-2,2-dimethylallyl-6,7-benzomorphan, 2-[4-(4'-

Fluoro)butyrophenone)-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan, 2'-Benzyloxy-2-allyl-5,9-dimethyl-6,7(H)benzomorphan hydrochloride, 5,9-Dimethyl-2-(3,3-dimethylallyl)-2'-benzyl-(alpha-14C)oxy-6,7-benzomorphan hydrobromide, 3,4,5,6-Tetrahydro-2,3-dimethyl-4-oxo-2,6-methano-2H-1,3-benzoxazocin-5-glyoxylic acid ethyl ester, 5-Carboxy-2-ethyl-2,6-methano-3-methyl-4-oxo-2,3,4,5,6-pentahydro-1,3-benzoxacine, 5-Acetyl-2-methyl-4-oxo-2,6-methano-2,3,4,5,6-pentahydro-1,3-benzoxazocine, 2,3-Dimethyl-4-thioxo-3,4,5,6-tetrahydro-2,6-methano-2H-1,3-benzothiazocin, 2-Ethyl-3,9-dimethyl-10-oxo-11-carboxy-2,4-(iminoethano)-3,4-dihydro-2H-1-benzopyran, 2,3-Dimethyl-4-oxo-2-ethano-2,3,4,5,6-pentahydro-1,3-benoxazocine-alpha-O-tosylacetic acid ethyl ester, 2,6-Methano-2,3-dimethyl-4-oxo-2,3,4,5-tetrahydro-6H-1,3-benzoxazocine, 2,9-Dimethyl-10-oxo-11-carbomethoxy-3,4-dihydro-2,4-(iminoethano)-2H-1-benzopyran, 2,3-Dimethyl-2,6-methano-4-oxo-2,3,4,5,6-pentahydro-1,3-benzoxazocine-5-carboxylic acid ethyl ester, 2-Phenyl-3-methyl-4-oxo-5-carboxy-2,6-methano-2,3,4,5,6-pentahydro-1,3-benzoxazocine, 5-(Ethoxycarbonylhydroxymethyl)-2,3,4,5-tetrahydro-2,6-methano-2-methyl-4-oxo-3-phenyl-6H-1,3-benzoxazocine, 1,4-Dioxo-5-(ethylcarbonylhydroxymethyl)-1,2,3,4,5,6-hexahydro-2,6-methano-2-methyl-3-phenyl-benzazocine, 2,3-Dimethyl-4-oxo-2,6-methano-2,3,4,5-tetrahydro-6H-1,3-benzoxazocine-5-[alpha-(4-tosyloxy)acetic acid], ethyl ester, 2-Methyl-4-oxo-3-phenyl-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocine, 6-Dimethyl-2,6-methano-4-oxo-2,3,4,5-tetrahydro-6H-1,3-benzoxazocine-5-carboxylic acid, 2-Ethyl-2,6-methano-3-methyl-4-oxo-2,3,4,5-tetrahydro-6H-1,3-benzoxazocine, 2-Ethyl-3,11-dimethyl-2,6-methano-2,3,4,5-tetrahydro-6H-1,3-benzoxazocin-4-one, 2,3-Dimethyl-4-oxo-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocine-5-glyoxylic acid, 3-Methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocine, 2,3-Dimethyl-2,6-methano-4-oxo-2,3,4,5-tetrahydro-6H-1,3-benzoxazocine-5-ylidene-5-(alpha-methoxy)acetic acid, ethyl ester, 2,3-Dimethyl-2,6-methano-4-oxo-2,3,4,5-tetrahydro-6H-1,3-benzoxazocine-5-(alpha-acetoxy)acetic acid, ethyl ester, 2-Methyl-3-phenyl-4-oxo-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocin-delta-5-alpha-acetic acid, 2-Methyl-3-phenyl-4-oxo-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocine-5-(alpha-acetoxyacetic acid ethyl ester), 2-Methyl-4-oxo-3-phenyl-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocine-5-phenylhydrazanoacetic acid ethyl ester, 2-Ethyl-3-hydroxy-4-oxo-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocine, 2-Methyl-3-hydroxy-4-oxo-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocine, 2-Methyl-4-oxo-3-phenyl-2,3,4,5-tetrahydro-2,6-methano-6H-1,3-benzoxazocine-delta-5-alpha-acetic acid ethyl ester, 2-Methyl-4-(methylamino)-2,3-dihydro-2,6-methano-1,3-benzoxazocine, 3,4,5,6-Tetrahydro-

3,6-dimethyl-2,6-methano-3-benzazocine, 1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(2,3-dihydroxy-3-methylbutyl)-2,6-methano-3-benzozocine-8-ol hydrochloride, 3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocin-8-yl-3-[(pyridinyl carbonyl)oxy] hydrochloride (or 2-(Cyclopropylmethyl)-5,9-dimethyl-3'-nicotinoyloxybenzomorphanhydrochloride (3:4) or 3-(Cyclopropylmethyl)-6,11-dimethyl-2,6-methano-8-nicotinoyloxy-1,2,3,4,5,6-hexahydrobenzazocine hydrochloride), 3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocin-8-yl 3-pyridinecarboxylate dihydrobromide (or 2-(Cyclopropylmethyl)-5,9-dimethyl-3'-nicotinoyloxybenzomorphan dihydrobromide) (+)-2-(Cyclopropylmethyl)-5,9-dimethyl-3'-nicotinoyloxybenzomorphan, hydrobromide (which has the common name Nicotinoyloxycyclazocine), N-Cyclopropylmethyl-5,9-dimethyl-3'-hydroxybenzomorphan (which has the common name, Cyclazocine), Ethylketocyclazocine methanesulfonate, Ketocyclazocine base, or (+/-)Bremazocine and the pharmaceutically acceptable salts, and hydrates thereof.

10. The method according to Claim 1 wherein the low affinity NMDA receptor antagonist is a compound according to the formula:



wherein

X is oxygen, sulfur, carbon, C=NOH or C=O;
R, R_1, and R_5 are independently selected from hydrogen or alkyl;
R_4 is hydrogen, =O or =S, alkyl, hydroxy, amino, or mono-alkyl amino;
R_3 is hydrogen, (optionally substituted) alkyl, (optionally substituted) hydroxyalkyl, alkenyl, dimethylallyl, (optionally substituted) aryl, (optionally substituted)arylalkyl, heteroarylalkyl, (optionally substituted) cycloalkylaryl, or hydroxy;
R_2 is hydrogen, hydroxy, alkoxy, arylalkyloxy, acetoxy, alkenyl, or 3-[(pyridinyl carbonyl)oxy];
R_6 is hydrogen, acetyl, carboxy, glyoxylic acid, glyoxylic acid ester derivatives, carbomethoxy, or ethoxycarbonylhydroxymethyl;

and pharmaceutically acceptable salts, provided that when X is carbon, R, R_4 and R_6 are hydrogen, R_1 and R_5 are methyl, and R_2 is hydroxy, R_3 can not be $CH_2CH=C(CH_3)_2$.

11. The method according to Claim 10 wherein the low affinity NMDA receptor antagonist is selected from 3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-8-yl-3-[(pyridinyl carbonyl)oxy]-3-benzazocine, metazocine, normetazocine, cyclazocine, norcyclazocine, alazocine, 1-N-allylnormetazocine, and phenazocine and pharmaceutically acceptable salts thereof.

12. A method of treating headaches and/or pain caused by cortical spreading depression, in a mammal, which method comprising administering to said mammal an effective amount of a low affinity NMDA receptor antagonist.

13. The method according to claim 12 wherein the low affinity NMDA receptor antagonist is selected from 3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-8-yl-3-[(pyridinyl carbonyl)oxy]-3-benzazocine, metazocine normetazocine, cyclazocine, norcyclazocine, alazocine, 1-N-allylnormetazocine, and phenazocine and pharmaceutically acceptable salts thereof.

FIG. 1A

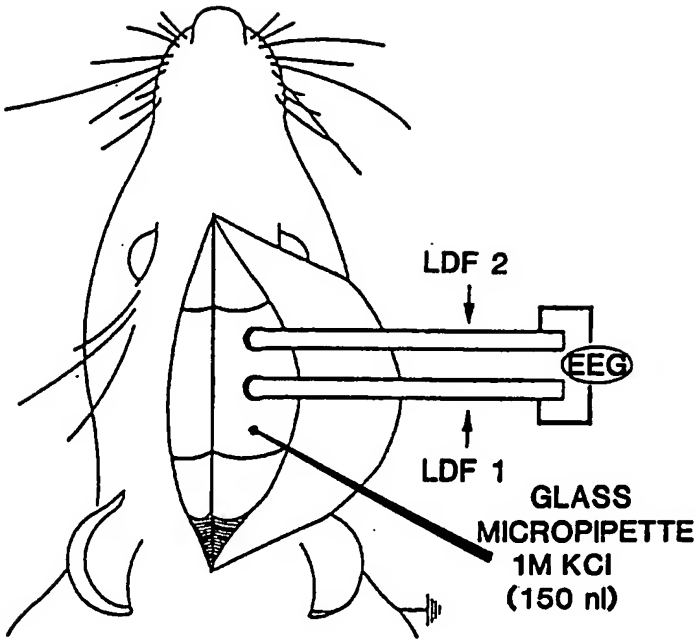
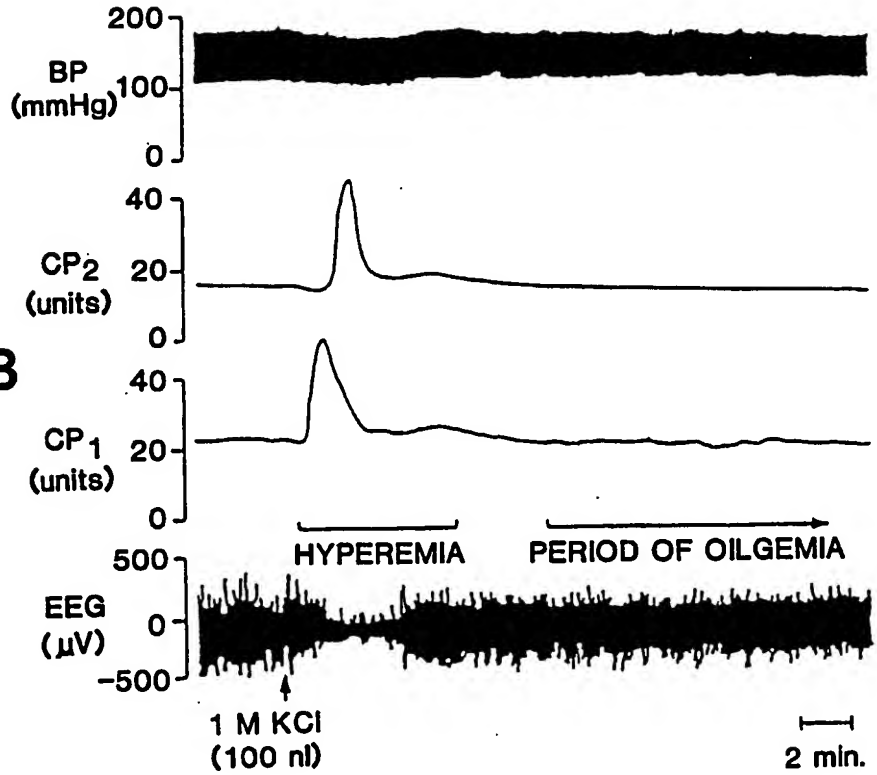


FIG. 1B



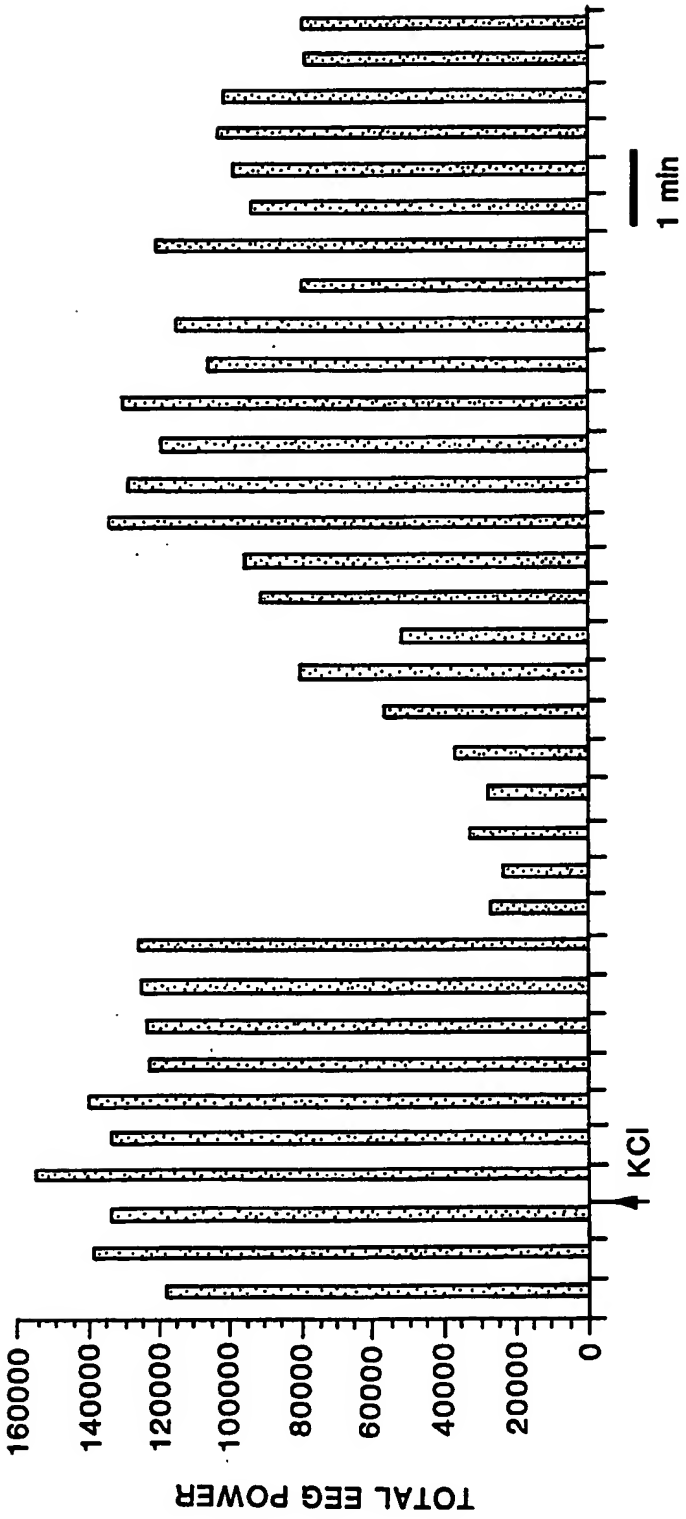


FIG. 2A

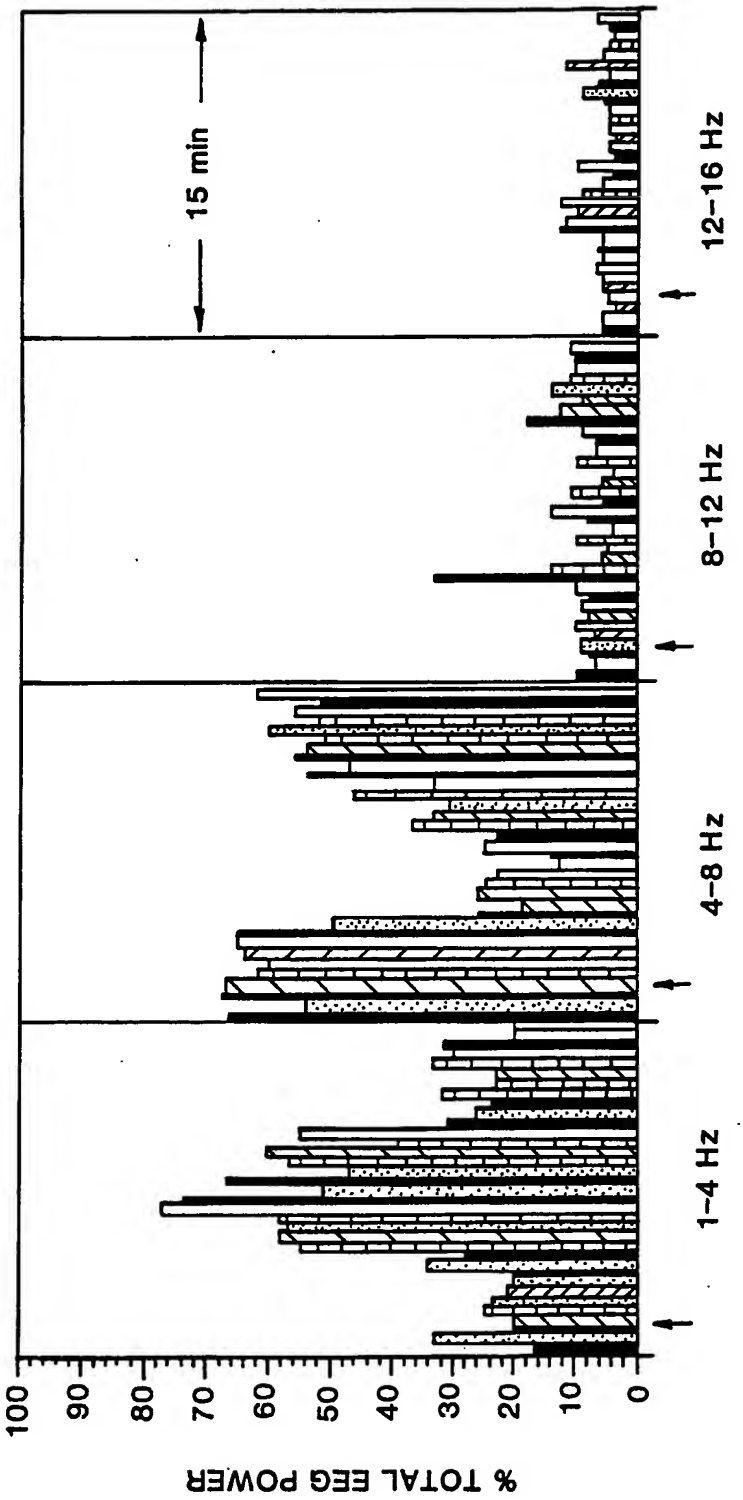


FIG. 2B

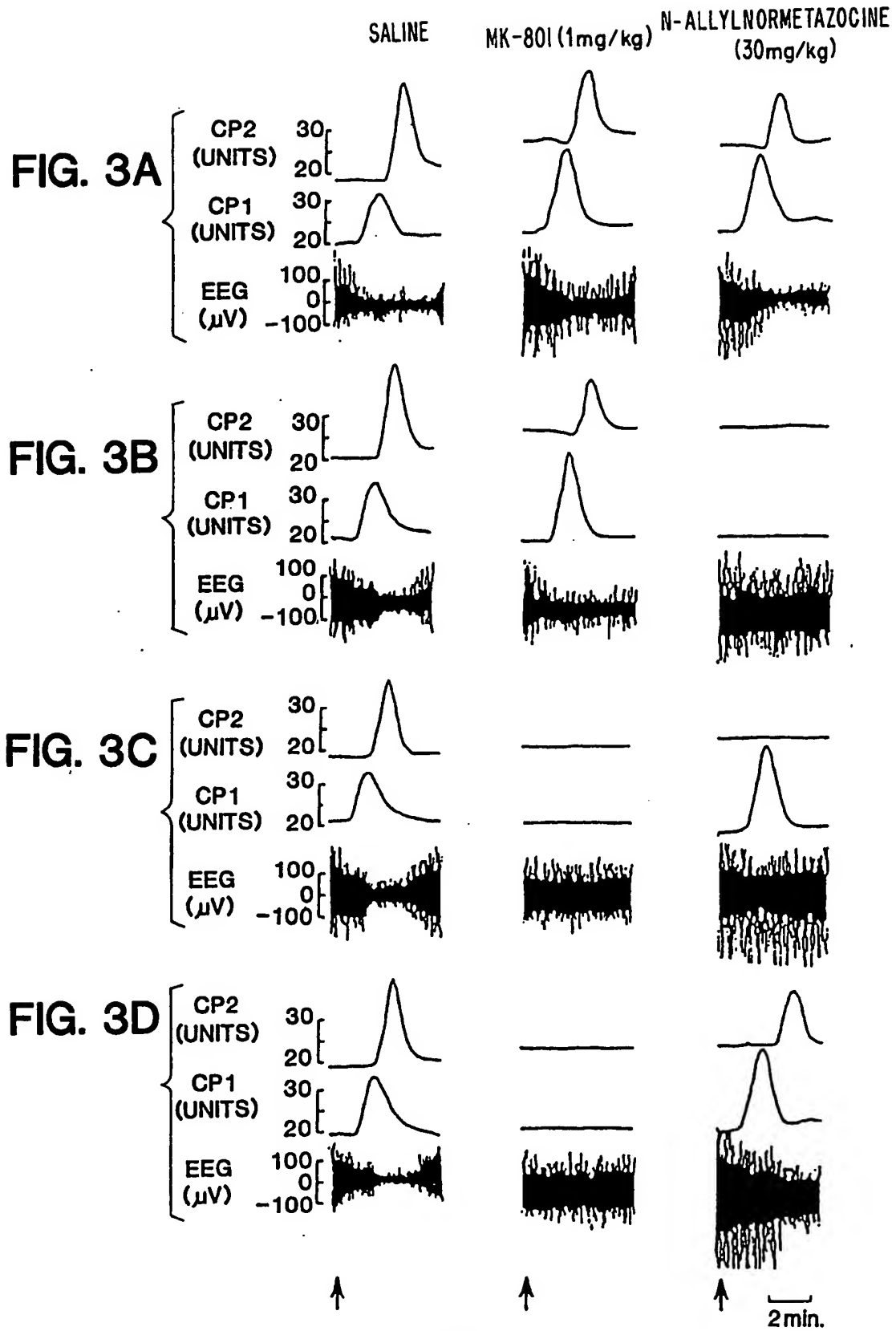


FIG. 3A

FIG. 3B

FIG. 3C

FIG. 3D

SUBSTITUTE SHEET (RULE 26)

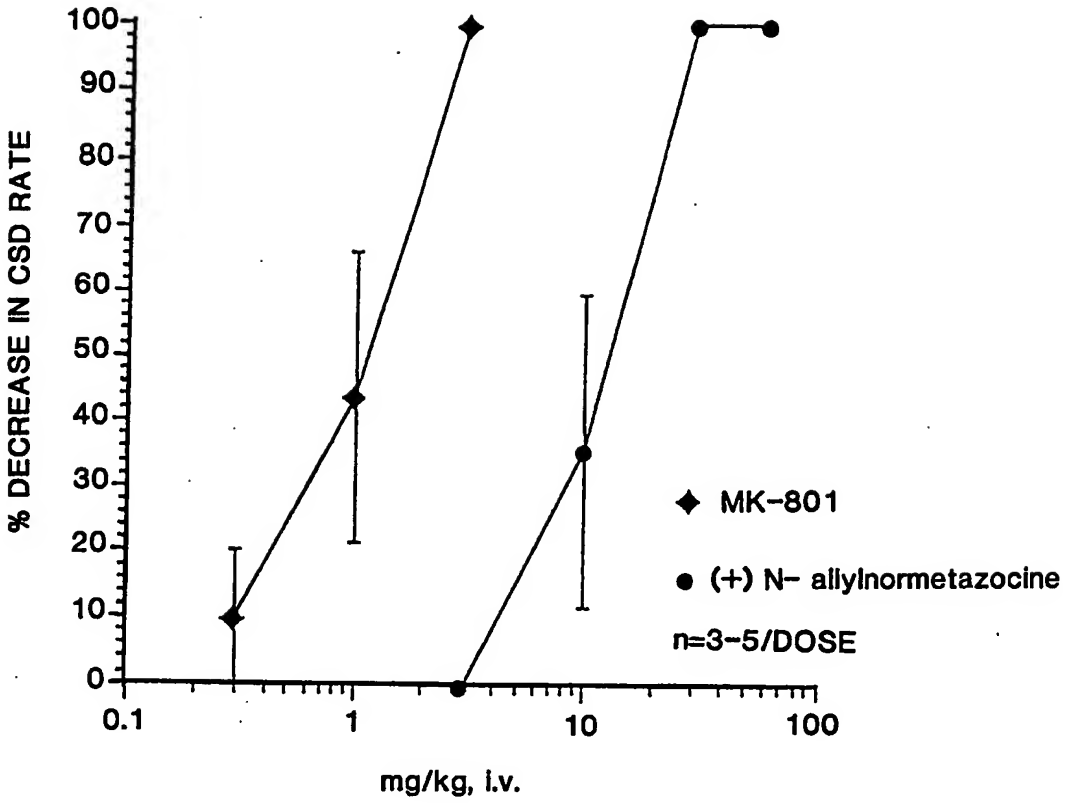


FIG. 4

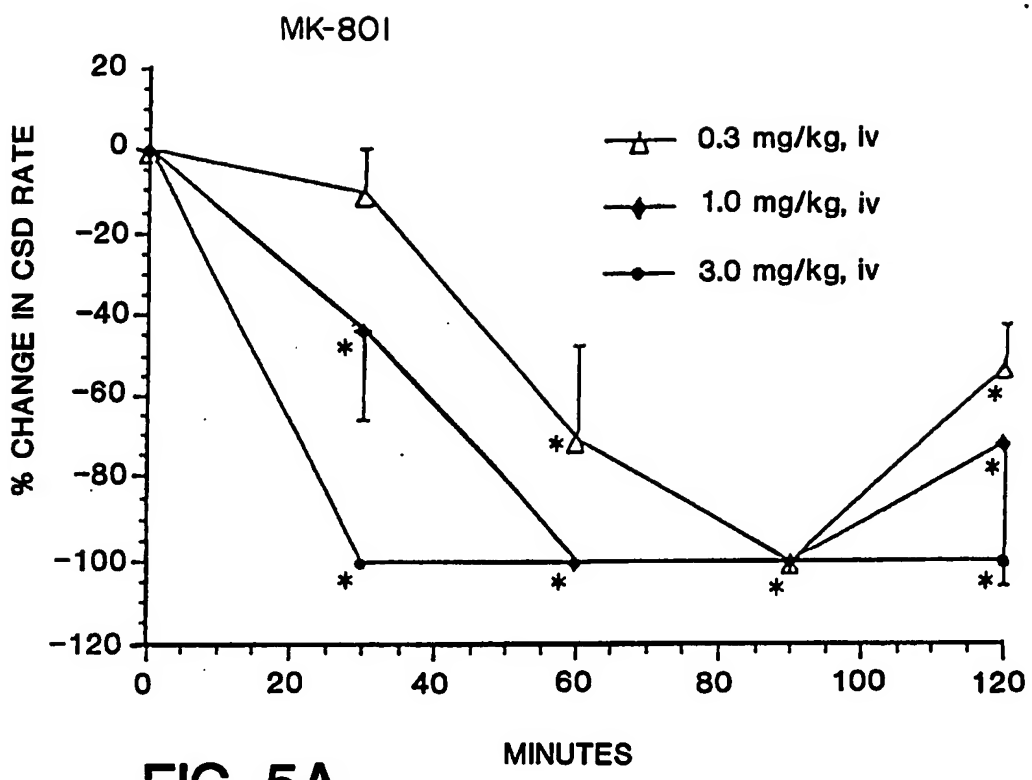


FIG. 5A

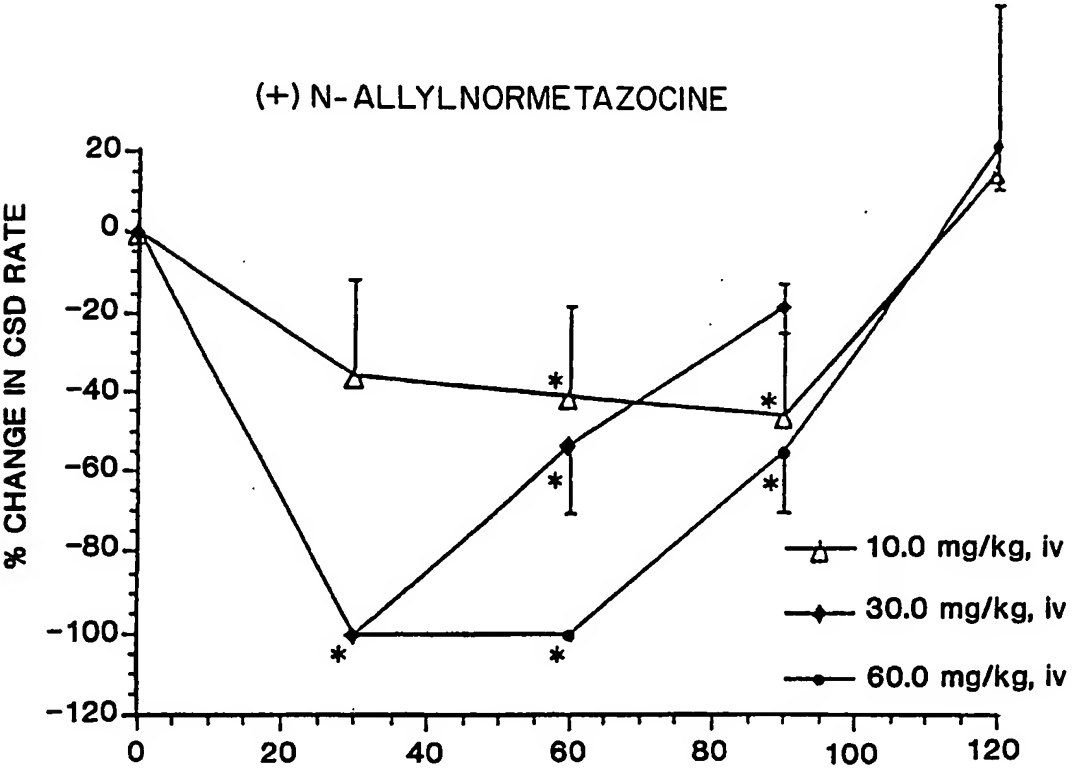


FIG. 5B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/09814

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/33, 31/38, 31/395
US CL :540/468, 477; 514/183, 431, 450
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/183, 431, 450

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

CAS online

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Stroke, vol. 23 (9), issued September 1993, LYSKO ET AL., "Neuroprotective Mechanism of (+) SKF 10,047 in vitro and in gerbil global brain ischemia", see pages 1319-1324.	1-14
A	J. Pharmacol. Exp. Ther., vol. 235(1), issued 1985, SNELL ET AL., "Antagonism of N-Methyl-3-Aspartate-Induced Transmitter Release in the Rat Striatum by Phencyclidine-Like Drugs and Its Relationship to Turning Behavior", pages 50-57.	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 31 OCTOBER 1994	Date of mailing of the international search report 19 DEC 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer PHYLLIS SPIVACK jd Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*